

ON THE ORIGIN OF CANCER.

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CASE.—On the 3d December 1872, at the request of her medical attendant, I visited Mrs B., aged fifty-four, who complained of a painful nodule in her right cheek. Having for a few years been in impaired health, she had in addition, for eleven months previous, suffered considerable annoyance from the sharp edge of a decaying tooth, the right middle molar in her lower jaw. To the irritation produced by this tooth she attributes the origin, in May of the above year, of the small painful tumour in the right cheek. The tumour had been gradually increasing in size, and the stinging paroxysmal pain in it had also increased to such an extent as seriously to disquiet her and interfere with her general health.

Upon examination, a tumour of about the size of a large pea was perceptible in the substance of the right cheek, opposite the situation in the lower jaw from which the offending tooth had been removed, and below the aperture of Stenon's duct. The tumour was not sharply circumscribed to the touch, and on being grasped in mass between the fingers its bulk seemed larger than as above described, but when carefully examined between the finger placed in the mouth and the thumb externally, it was apparent that there was a limited zone of indurated tissue immediately surrounding the nucleus of the growth, which latter was of firmer consistence and of the size indicated above, from one-fourth to five-sixteenths of an inch in diameter, rounded in form, painful when much handled, and yet not very tender on compression. Its situation seemed to be

EXPLANATION OF THE PLATE.

Section of Cancer of the Cheek tinted with Carmine, $\times 50$ diameters.

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| <i>a.</i> Normal hairs. | <i>d, d.</i> Hyperplastic hair-follicles. |
| <i>a'.</i> Brittle hairs from hyperplastic follicles. | <i>e.</i> Sections of vessels. |
| <i>b.</i> Normal epidermis, skin, and hair-follicles. | <i>f.</i> Adipose tissue. |
| <i>c.</i> Hyperplastic Malpighian layer of epidermis. | <i>f'.</i> Adipose tissue infiltrated with cancer. |
| | <i>g.</i> Cancerous tumour. |
| | <i>h, h.</i> Muscle. |

nearer the mucous than the cutaneous surface, immediately external to the buccinator muscle; and, though more distinctly felt from the mucous than from the cutaneous surface, it was more intimately connected with the latter, the mucous membrane being loose and displaceable over it, while the skin, although capable of being grasped from the outside independently of the tumour, was felt to be connected with it by a certain amount of induration. The tumour produced a distinct increase of thickness in the part where it was situated, being visible as a prominence on the cheek when looked at obliquely. The skin over the prominence had a faint bluish-red tint, and appeared to the naked eye slightly altered in texture. The glands in front of the ear and beneath the horizontal ramus of the jaw were of natural size.

The suspicious history and appearance of the tumour induced us to decide upon its removal, and on the 5th December 1872, she was placed under the influence of ether, and the growth, along with the skin and tissues included between two elliptical incisions directed from before backwards, dissected out and removed. The portion of the buccinator muscle with which it was in contact was removed along with it, but the buccal mucous membrane was not opened, so that the wound communicated only with the cutaneous aspect of the cheek. The supervention of sickness, from her having inadvertently partaken of food prior to the operation, caused some delay in controlling the hæmorrhage from three arteries which had been divided; but these were eventually secured by torsion, and the wound was closed by five silk sutures. On the third day the sutures were removed, the wound was found quite healed upon the fifth day, and she made a very good recovery.

On the 11th January 1873, the tumour had recurred in the same situation. It was again removed on the 17th January, and no recurrence is observable up to the present date.

Microscopic Examination.—The tumour was hardened in dilute chromic acid, and afterwards sections through its whole extent, including the skin, were examined before and after being tinted in solution of carmine. It proved to be an example of true carcinoma, with a large predominance of the groups of cancer-cells and a relatively small proportion of the connective tissue trabeculae. Examined under a low power, the nucleus of the growth (see Plate, *g*) was seated immediately external to the fibres of the buccinator muscle (*h*, *h*), and although pretty well circumscribed, was found to have invaded the connective tissue in its vicinity, causing a certain amount of disappearance of the fat-cells (*f*) filling the alveoli, wherever the invasion had advanced so as to be decidedly evident. Its connexion with the skin was produced by dense connective tissue with cancerous cellular proliferation and pronounced disappearance of the fatty alveoli, so that the low power exhibited one principal and several subordinate bands of indurated and infiltrated connective tissue passing directly between tumour

and skin. At the spot corresponding with these bands the tissue of the true skin was thickened, chiefly by hyperplasia of its connective elements, but partially also by a slight amount of cancerous invasion. The epidermis in this locality was increased in thickness to double that which it presented on the adjacent portions of the skin, and this hypertrophy of the epidermis was chiefly produced by the deeper layers (*c*), which were unusually soft and succulent. The hair-follicles (*d*, *d'*) shared in this hypertrophy, their epidermic lining being considerably more voluminous, and the follicles extending much deeper inwards towards the infiltrated bands than was the case in the parts of the skin which were more remote and uninvolved in the alteration. The hairs themselves presented little difference from those of the healthy skin, seeming only to be more brittle (*a'*) and to break across more readily than was the case elsewhere (*a*).

Remarks.—The most remarkable feature revealed by the microscopic examination of the tumour from the above case, exists undoubtedly in the disturbance of nutrition revealed in the epidermic structures of the skin, sympathetic with the origin and progress of the deeper tumour. The unusually early period of its existence at which the tumour was discovered and removed, and the fact that it was as plainly an example of deep-seated cancer (as distinguished from epithelioma or epithelial cancer) as those ordinarily met with in the mammary gland and elsewhere, render the case of considerable value as bearing upon the inquiry concerning the origin and nature of cancer, which at present is occupying so much the attention of pathologists. I have hence selected it as a type of other observations which I have made in this matter, and which will be referred to afterwards.

It will be remembered that Virchow was the first to insist on the *epithelial* character of the cells, which, in cancer, fill up the alveolar interspaces of its connective tissue framework; and it seems strange that this great observer, instead of applying to these cells his own maxim, that *the individual constituents of a tumour, wherever found, bear the imprint of the tissue from whence they were derived*, should have adopted the view that they were produced from connective tissue, and that consequently both the constituents of cancer, framework and cell-masses, had their origin from this tissue alone.

Thiersch in Leipzig, in the year 1865, drew attention to epithelial cancer, which we in England call epithelioma, claiming for its cells a totally different origin from that assigned by Virchow. He pointed out that epithelium is a product of the two external germinal layers of the embryo; that, according to His, Acby, and others, the division into layers which exists in the embryo after a certain stage of development, persists in the completed individual so unalterably that epithelium is incapable of being produced by the connective-tissue structures (middle germinal layer), or connective structures

of being produced from epithelium; and hence that the origin of epithelium must always be sought in pre-existing epithelium. Arguing farther on the admittedly epithelial nature of the masses which, in epithelial cancer, fill the large interspaces between the hypertrophic papillæ and among the connective-tissue trabeculæ, he sought to prove that it was simply a disease arising from proliferation of pre-existing epithelium. He was successful in attaching extreme probability to his views, and they would doubtless have been more generally accepted but for the controversy then raging concerning the reproduction of destroyed epithelium. This controversy is not yet at an end, but there is little doubt how it must terminate.

Billroth, Waldeyer, and others, took up the matter where Thiersch had left it, and applied his deductions to every species of cancer, asserting that every such tumour takes its origin from some portion of the rete Malpighii of the epidermis, or from the mucous epithelium, or true glandular epithelium (but not from the cells of the lymphatic glands), where these cells, multiplying by division and possessing the known characters of young epithelial cells—viz., spontaneous (amoeboid) movement and power of wandering, and consisting of nucleus and protoplasm unfettered by cell-wall—push their way among the neighbouring connective tissue, proliferate there, and send their progeny further; thus producing the nests of cells so characteristic of the true cancer structure. In a brief period the original focus has ramified in all directions, its sprouts penetrating hither and thither among the connective tissue, which becomes so permeated with epithelial offshoots that, on section, the latter appear like the pores of a sponge. The young cancer-cells thus wandering about possess the property of multiplying indefinitely by subdivision, but cannot excite the connective tissue to more participation than would be the result of similar mechanical interference of any other sort. When they find their way into the lymphatics they excite no corresponding proliferation in the endothelium of those vessels, and when arrested in the lymphatic glands the infiltration which speedily follows is produced by their unaided activity. They have not the power of infecting distant epithelium, and stimulating it to similar proliferation; when carried, for example, to the liver, the gland-cells of that organ, although epithelial in their nature, do not partake in the proliferation which follows in the interlobular spaces. Such views as these, so consonant with all the pathological principles indicated by Virchow and his followers, have attracted the attention of a multitude of pathologists, who, acknowledging their accuracy and beauty, have now adopted them, and form the school of thinkers most advanced in the domain of cancer pathology.

Many others, while admitting the epithelial origin of epithelial cancer, hold a different source of development as possible for other forms, viz., Thiersch, Klebs, Rindfleisch, Neumann, Volkmann, etc. But, even among these observers, there are many admissions of the

derivation of non-cutaneous cancers from epithelium. Thus, Birch-Hirschfeld admits it in the testicle, Neumann in the mamma, etc.

The party who totally deny its origin from epithelium, and trace it in every case to other tissues, are Virchow, Förster, W. Müller, Köster, Classen, etc. Köster thinks cancer-cells arise from the endothelium of the lymphatics, and believes he found this development demonstrated in lymphatic vessels treated by silver solutions. Classen, basing his judgment on one case of corneo-sclerotic canceroid, makes the cancer-cells proceed from the amœboid white blood-corpuscles which have wandered out into the tissues. Virchow, Förster, and Müller, seek the origin of cancer in the connective-tissue structures generally.

The arguments used by the party of Waldeyer and Billroth deserve to be mentioned at length. In the *first* place, *cancer is never found as a primary disease except where epithelium exists*. Thus the brain, the bones, the heart, the diaphragm, the spleen, and the lymphatic glands, structures where epithelium does not normally exist, are never the seat of the primary disease, and the few cases which have been cited in opposition to this statement are easily disposed of on the probable explanations of their unobserved involvement from epithelial structures (as in Paget's case of canceroid of the inguinal glands, Virchow's cancer of the tibia, etc.), or of the abnormal occurrence of dermoid cysts, which are congenital invaginations of the external germinal layer. These last have actually been demonstrated as producing cancer in non-epithelial situations by Corril, Lücke, and Czerny. Were Köster's derivation from lymphatics the true one, such structures as the above could not enjoy such an immunity from cancer, and such a proclivity to the various forms of sarcoma, a growth invariably of connective tissue origin.

Secondly, In the human body, after it has advanced beyond the early embryonic stage, *epithelium never develops into, or is developed from, other tissues*. Waldeyer points out that the chief characteristic of the epithelial cell is, that, whatever form it may assume, it has never an organic connexion with a neighbouring cell. Processes and prolongations it may have, but these only intermingle, never fuse together, with those of neighbouring cells. Hence the cancer-cells are indubitably epithelial, and must have their origin from the epithelial layers.

Thirdly, *Epithelial tissue possesses neither bloodvessels nor lymphatics*, and these are also never found in the masses of cancer-cells, but only in their connective-tissue framework. It is sometimes observed that a vessel seems to pass into or through a mass of intra-alveolar cancer-cells, but close observation always shows such a vessel to be surrounded by a sheath of connective tissue and not lying naked among the cells. Waldeyer also has shown that, where inflammatory processes are set up in cancer tumours, suppuration occurs in the connective-tissue framework, while the cancer-

cell masses are not affected—another confirmation of their epithelial nature.

Fourthly, Epithelial tissue possesses no fibrous, albuminous, or cartilaginous intercellular substance, such as is found in the connective-tissue structures; it sometimes, on the other hand, exhibits between its cells cementing substance, which may become horny, colloid, or mucous. In colloid cancer the cells and cementing substance have undergone the colloid metamorphosis, the cells sometimes disappearing to a great extent. Mucin is a product of both epithelium and connective tissue. Albumen, cartilage, and fibrine, are the products of connective tissue alone. The transformations of the cancer-cell masses, and their products, bear out, in this point of view, their epithelial nature.

Fifthly, Epithelial cells reproduce themselves by cell division, and the young cells so produced possess spontaneous (amoeboid) movements, and the power of sending out processes and of wandering from the place where they were formed. Hence we have an explanation of the extension and metastasis of cancer. Several observers have noted the amoeboid movements of young cancer-cells, which, in some forms, are found at an early period in the lymphatics, whence they travel to the lymph-glands. These in turn becoming the basis of the cancerous proliferation, the disease extends further along the lymphatics, and in time reaches the venous circulation, and then the dissemination of cancer becomes general over the whole frame. Sarcoma extends usually by the bloodvessels, and hence its metastases are commonly observed in the internal organs, as in the lungs, seldom in the lymphatics. Some forms of cancer do not involve the lymphatics at an early period. Thus, epithelial cancer and rodent ulcer are long confined to their place of origin.

Sixthly, The investigation of large numbers of primary cancerous tumours (Waldeyer, in his second article on the subject, cites 203 examined by himself) confirms in every point their origin from pre-existing epithelium, while the examination of equally large numbers of tumours from non-epithelial organs and structures demonstrates in every case their inability to become the seats of primary cancer.

In addition to these reasons, I would call attention to the behaviour of the epithelial tissues in the immediate vicinity of cancerous growths, which I have found invariably in a state of altered nutrition. *The epithelium, even though not actually cancerous, is in an abnormal state of hyperplasia, and seems ready itself, by a slight increase of activity, to reproduce the disease* when the chief focus has been removed, or to participate in its extension when it is allowed to remain.

In the case of cancer in the neighbourhood of the true skin—as on the prepuce, the lips, the face, the hands, etc.—one of the earliest expressions of the disease is a recognisable amount of hypertrophy of

the epidermis over the tumour, and a binding down of this structure, so that it cannot be moved backwards and forwards over it. This is equally true whether the cancerous proliferation of epithelium progresses more superficially on and between the papillæ of the skin, so as to give rise to an elevated epithelioma, or extends among the subcutaneous tissue or deeper parts, so as to form a cancerous nodule of the ordinary deep description; in both classes of cases, the skin is bound down to the tumour from the very commencement, and generally presents an alteration of appearance visible to the naked eye of a close observer. The cuticle appears rough and scaly, and the true skin beneath shows through it with a purplish red tinge, so that the portion affected offers a contrast to that in its vicinity—not very prominent, it is true, but unmistakable on close observation. The hairs are sometimes stunted and broken, the hair-follicles hypertrophied, and the sweat-ducts present a thickening of their epithelial lining. In the case described at the commencement of this paper, several sweat-ducts were thus altered, although none were met with in the section from which the drawing was taken. I formed the impression that the tumour had arisen from a sweat-gland.

Where cancer arises from the epithelium of mucous membranes; the same hyperplastic condition is observed. In cancers of the tongue, gums, etc., which I have examined, a prominent feature under low powers has always been a greatly increased thickening of the epithelium, involving even the mucous glands; and in every case of cancer within the mouth which I have seen, the adherence and immobility of the epithelium has been a marked feature, and a good diagnostic sign. In cancers of the cervix uteri, I have been convinced of the epithelial origin of both forms; as well of that which, confining itself to the surface, spreads into the cauliflower growth of hypertrophic papillæ, separated by hyperplastic epithelium, as of the deeper form, which, still retaining its connexion with the patch of superficial epithelium (rough, hyperplastic, and immovably fixed to the tumour beneath), extends into the substance of the uterus as a circumscribed knot, differing in appearance from, although claiming the same origin as, the cauliflower epithelioma.

In cancers of the mamma, which arise primarily from the epithelial lining of the acini and tubules of the gland, the hyperplasia appears to extend along the tubules, and produce the early retraction of the nipple so prominent in this disease. In a mammary gland I recently removed, where a knot of scirrhus was embedded in a mass of encephaloid cancer, I believe I could clearly trace the hypertrophy of the epithelial lining of the tubules into the nipple itself.

It may be urged that such changes in the epithelium near cancer are nothing more than the results of the increased vascularity and slight inflammatory action produced by the pain and irritation usually present with such growths. But a closer examination of

the seat and nature of these changes will dispel this idea. The epithelium is not found altered everywhere in the neighbourhood of the tumour, but only at the part from which it took its rise. There is frequent occasion to observe this in the cheek, lips, and other parts of the body where skin and mucous membrane run parallel to each other, and enclose between them connective tissues. In such case it is usually possible to diagnose whether the cancer arose from skin or mucous surface, as it is at first adherent only to its focus of origin where the epithelial alterations are also observable. Not unfrequently the origin can be recognised as having been cutaneous, though the tumour has its seat apparently nearer the mucous surface—the former being fixed, the latter free. The Malpighian layer (*c*) is mainly affected in the epithelial hyperplasia; without multiplication of the nuclei of its cells, it is thicker and more succulent; it supports the likewise thickened layer superficial to it, and is accompanied by increased proliferation in the epithelial appendages of the skin. Sweat-ducts are in a state of enlargement plainly due to the hyperplasia of their epithelial linings, and the hair-follicles (*d, d*), from a similar cause, are larger and longer than usual, extending into the skin and subcutaneous tissue to an unwonted depth. The hairs (*a'*) are more brittle than normal. The papillæ of the skin (or mucous membrane) are not hypertrophied nor separated by hypertrophic epithelium to the extent seen in epithelial cancer proper, and this different behaviour of the papillæ forms a marked distinction between this latter and the alterations I have attempted to indicate.